Complete Summary

GUIDELINE TITLE

Use of nonsteroidal antiinflammatory drugs: an update for clinicians. A scientific statement from the American Heart Association.

BIBLIOGRAPHIC SOURCE(S)

Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA, American Heart Association. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. Circulation 2007 Mar 27;115(12):1634-42. [54 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

- June 15, 2005, COX-2 Selective (includes Bextra, Celebrex, and Vioxx) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): Labeling revised to include a boxed warning and a Medication Guide, highlighting the potential for increased risk of cardiovascular (CV) events and life-threatening gastrointestinal (GI) bleeding.
- April 7, 2005, Bextra (valdecoxib), Cox-2 inhibitors, Celebrex (celecoxib), Non-steroidal anti-inflammatory drugs (NSAIDS) (prescription and OTC, including ibuprofen and naproxen: Bextra (valdecoxib) withdrawn from the market and labels for other Cox-2 inhibitors and NSAIDS revised to include a boxed warning and a Medication Guide, highlighting the potential for increased risk of cardiovascular (CV) events and life-threatening gastrointestinal (GI) bleeding.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Musculoskeletal symptoms or other conditions requiring nonsteroidal antiinflammatory drug (NSAID) therapy
- Cardiovascular disease or increased risk of cardiovascular disease

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Cardiology
Family Practice
Internal Medicine
Pharmacology

INTENDED USERS

Advanced Practice Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To provide updated recommendation for the use of nonsteroidal antiinflammatory drugs (NSAIDs) in patients with known cardiovascular disease or risk factors for ischemic heart disease

TARGET POPULATION

Patients with musculoskeletal symptoms with known cardiovascular disease or risk factors for ischemic heart disease taking nonsteroidal antiinflammatory drugs (NSAIDs)

INTERVENTIONS AND PRACTICES CONSIDERED

Stepped care approach to pharmacologic therapy including:

1. Acetaminophen, aspirin, tramadol, narcotic analgesics (short term)
2. Nonacetylated salicylates

3. Non cyclooxygenase (COX)-2 selective nonsteroidal antiinflammatory drugs (NSAIDs)
4. NSAIDs with some COX-2 activity
5. COX-2 selective NSAIDS
6. Addition of aspirin and proton pump inhibitors (PPIs) for patients at increased risk of thrombotic events receiving NSAIDs
7. Regular monitoring for side effects of NSAIDs
8. Reduction of the dose or discontinuation of the offending NSAID

MAJOR OUTCOMES CONSIDERED

- Adverse effects of nonsteroidal antiinflammatory drugs (NSAIDs)
- Safety and efficacy of NSAIDs

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review
Review of Published Meta-Analyses

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Expert peer review of American Heart Association (AHA) Scientific Statements is conducted at the AHA National Center.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on December 20, 2006.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Recommendations for Management

From both the patient's and the physician's perspectives, the problem lies in balancing the risks and benefits of medications for pain relief. Of course, this is not unique to these medications, but their use highlights the issues to be considered. Below are several questions that should be considered when one makes treatment decisions about pain medications in patients with or at high risk for cardiovascular disease. A suggested stepped-care approach to management of patients with musculoskeletal symptoms is shown in Figure 7 in the original guideline document and discussed in detail below.

What Are the Treatment Considerations?

Musculoskeletal symptoms should be categorized as those that result from tendonitis/bursitis, those that result from degenerative joint problems (e.g., osteoarthritis), or those that result from inflammatory joint problems (e.g., rheumatoid arthritis). Initial treatment should focus on nonpharmacological approaches (e.g., physical therapy, heat/cold, orthotics).

For patients whose symptoms are not controlled by nonpharmacological approaches, pharmacological treatments should then be considered. When choosing any medication, both safety and efficacy should be considered. In general, the least risky medication should be tried first, with escalation only if the first medication is ineffective. In practice, this usually means starting with acetaminophen or aspirin at the lowest efficacious dose, especially for short-term

needs. Despite the potential for abuse, a role remains for narcotic medications for short-term pain relief. It should be recognized that with the exception of aspirin, the "low-risk" medications mentioned above have not been subjected to randomized clinical trials to conclusively demonstrate their superior safety.

In patients who do not tolerate these simple interventions or who require long-term or high-dose therapy, the issues become more complex. Long-term or high-dose therapy with aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) is associated with increased risk for gastrointestinal (GI) bleeding. Occasionally, high-dose acetaminophen can result in hepatic toxicity, especially in patients who consume excess alcohol. When acetaminophen, aspirin, and perhaps even narcotic medications (for acute pain) are not effective, tolerated, or appropriate, it may be reasonable to consider an NSAID as the next step; however, this should be coupled with the realization that effective pain relief may come at the cost of a small but real increase in risk for cardiovascular or cerebrovascular complications (see Figure 7 in the original guideline document).

The scientific evidence to date (see the Table in the original guideline document titled "NonSelective NSAIDs and Cardiovascular [CV] Risk") indicates that important differences exist between these agents in terms of risk of major thrombotic events. Clinicians are cautioned against relying on meta-analyses that involve an incomplete set of trials, contain small numbers of events, and focus only on short-term follow-up when assessing the relative risks of various agents. Naproxen appears to be the preferred choice.

What Patient Characteristics Should Be Considered?

Patients with a history of or risk for GI bleeding, especially in relation to aspirin or other nonspecific NSAID use, might be given acetaminophen initially. Alternatively, proton-pump inhibitors may diminish the risk of recurrent GI bleeding in subjects who require low-dose aspirin. If these alternatives are not possible, it may be reasonable to consider a cyclooxygenase (COX)-2 inhibitor if the potential benefits of treatment are believed to outweigh the potential cardiovascular risks. Patients who are tolerant of nonspecific NSAIDs but find them insufficient could also consider a COX-2 inhibitor.

Patients with or at risk for active atherosclerotic processes, including those with recent bypass surgery, unstable angina or myocardial infarction, or ischemic cerebrovascular events, have greater increases in absolute risk for adverse cardiovascular effects when given a COX inhibitor. (It is difficult to provide precise estimates of the absolute increase in risk because the excess number of events is related to such factors as the underlying risk of the patient, the relative risk of the drug, and the duration of follow-up). In these patients, prudence dictates extra caution in the use of COX-2 inhibitors, which should include the use of only the recommended doses and for the shortest period of time required to control symptoms. Every effort should be made to assess and treat modifiable risk factors before and during NSAID treatment. COX inhibitors can lead to impaired renal perfusion, sodium retention, and increases in blood pressure, which may contribute to their adverse cardiovascular effects. Renal function and blood pressure should be monitored in subjects taking COX-2 inhibitors. This is especially true when these drugs are given to subjects with preexisting

hypertension, renal disease, and heart failure (see Figure 7 in the original guideline document).

If You Use a COX-2 Inhibitor, Does Selectivity Matter?

The available data have implicated several COX-2 inhibitors with varying degrees of selectivity. As suggested by the data summarized in the Table, Figure 1, and Figure 6 of the original guideline document, even a relative lack of COX-2 selectivity does not completely eliminate the risk of cardiovascular events, and in that regard, all drugs in the NSAID spectrum should only be prescribed after thorough consideration of the risk/benefit balance. Additional data bearing on this issue will be provided in the ongoing PRECISION trial (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen; http://www.clinicaltrials.gov, No. NCT00346216), which is randomizing patients with rheumatoid arthritis or osteoarthritis to celecoxib, ibuprofen, or naproxen, the latter being 2 NSAIDs that are further toward the non-COX-2 end of the spectrum (see Figure 6 in the original guideline document).

Can Patients Using Aspirin for Cardioprotection Also Use NSAIDs or Selective COX-2 Inhibitors for Pain Relief?

Evidence indicates that ibuprofen, but not rofecoxib (a COX-2 inhibitor), acetaminophen, or diclofenac, interferes with aspirin's ability to irreversibly acetylate the platelet COX-1 enzyme, and it would be expected, although it has not been proved, that this would reduce the protective effect of aspirin on risk for atherothrombotic events. Per an U.S. Food and Drug Administration (FDA) advisory:

> "Patients taking immediate release low-dose aspirin (not enteric coated) and ibuprofen 400 mg should take the ibuprofen at least 30 minutes after aspirin ingestion, or at least 8 hours before aspirin ingestion to avoid any potential interaction. . . . Recommendations about concomitant use of ibuprofen and enteric-coated low dose aspirin cannot be made based on available data. One study showed that the antiplatelet effect of enteric-coated low dose aspirin is attenuated when ibuprofen 400 mg is dosed 2, 7, and 12 hours after aspirin."

Of note, the combination of aspirin (necessary for protection against cardiovascular events) and a coxib may ameliorate the gastric mucosal protective effect of COX-2 inhibition. The combination of the two may also prolong the time for recovery from gastric mucosal injury.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of nonsteroidal antiinflammatory drugs (NSAIDs) in patients with known cardiovascular disease or those at risk for ischemic heart disease

POTENTIAL HARMS

- Current evidence indicates that selective cyclooxygenase (COX)-2 inhibitors have important adverse cardiovascular effects that include increased risk for myocardial infarction, stroke, heart failure, and hypertension. The risk for these adverse effects is likely greatest in patients with a prior history of or at high risk for cardiovascular disease. In these patients, use of COX-2 inhibitors for pain relief should be limited to patients for whom there are no appropriate alternatives, and then, only in the lowest dose and for the shortest duration necessary.
- COX inhibitors can also lead to impaired renal perfusion, sodium retention, and increases in blood pressure, which may contribute to their adverse cardiovascular effects.
- Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with a small but real increase in risk for cardiovascular or cerebrovascular complications
- Common side effects of NSAIDs (with varying relative frequencies) are gastrointestinal (GI) ulceration, inhibition of platelet aggregation, inhibition of uterine motility, inhibition of prostaglandin-mediated renal function, and hypersensitivity reactions.
- High-dose acetaminophen can occasionally result in hepatic toxicity, especially in patients who consume alcohol.
- Ibuprofen, if taken concomitantly with aspirin, may reduce the protective effect of aspirin on risk for atherothrombotic events.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2007 Mar 27

GUIDELINE DEVELOPER(S)

American Heart Association - Professional Association

SOURCE(S) OF FUNDING

American Heart Association

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: Elliott M. Antman, MD, FAHA; Joel S. Bennett, MD; Alan Daugherty, PhD, FAHA; Curt Furberg, MD, PhD, FAHA; Harold Roberts, MD, FAHA; Kathryn A. Taubert, PhD, FAHA

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Ownership Interest	Consultant/ Advisory Board	Other
Elliott M. Antman	Brigham and Women's Hospital, Harvard Medical School	None	None	None	None	None	None
Joel S. Bennett	University of Pennsylvania	None	None	None	None	None	None
Alan Daugherty	University of Kentucky	None	None	None	None	None	None
Curt Furberg	Wake Forest University	None	None	None	None	None	None
Harold Roberts	University of North Carolina	None	None	None	None	None	None
Kathryn A. Taubert	American Heart Association	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Heart Association Web site.

Print copies: Available from the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596; Phone: 800-242-8721

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI Institute on June 5, 2007. The information was verified by the guideline developer on July 23, 2007.

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